Dose optimization of piperacillin/tazobactam in critically ill children

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Synopsis

Objectives. The aim of this study was to characterize the population pharmacokinetics of piperacillin and tazobactam in critically ill infants and children, in order to develop an evidence-based dosing regimen.

Patients and Methods. This pharmacokinetic study enrolled patients admitted to the paediatric ICU for whom intravenous piperacillin/tazobactam (8:1 ratio) was indicated (75 mg/kg q6h based on piperacillin). Piperacillin/tazobactam concentrations were measured by a liquid chromatography-tandem mass spectrometry method. Pharmacokinetic data was analysed using nonlinear mixed effects modelling.

Results. Piperacillin and tazobactam blood samples were collected from 47 patients (median age: 2.83 years; range: 2 months - 15 years). Piperacillin and tazobactam disposition was best described by a two-compartment model which included allometric scaling and a maturation function to account for the effect of growth and age. Mean clearance estimates for piperacillin and tazobactam were 4.00 L/h and 3.01 L/h for a child of 14 kg. Monte Carlo simulations showed that an intermittent infusion of 75 mg/kg (based on piperacillin) q4h over 2 hours, 100 mg/kg q4h given over 1 hour or a loading dose of 75 mg/kg followed by a continuous infusion of 300 mg/kg/24h were minimally required to achieve the therapeutic targets for piperacillin (60 % $fT_{>MIC}$>16 mg/L).

Conclusion. Standard intermittent dosing regimens do not ensure optimal piperacillin/tazobactam exposure in critically ill patients, thereby risking treatment failure. The use of a loading dose followed by a continuous infusion is recommended for treatment of severe infections in children >2 months of age.

INTRODUCTION

Paediatric sepsis and septic shock reportedly affect 30% of children admitted to paediatric ICU, with a 25% mortality rate.[1] Early intervention with appropriate antibiotic treatment remains a cornerstone in the pharmacological treatment of those children.

Piperacillin/tazobactam is a broad-spectrum β-lactam antibiotic commonly used in the paediatric ICU for (empirical) treatment of severe infections. Typical indications include ventilator-associated pneumonia, intra-abdominal infections and sepsis of unknown origin. Despite its use, only treatment of intra-abdominal infections in children older than 2 years is currently approved by the European Medicines Agency.[2] This means that clinical practice still represents off-label use of this drug combination in younger paediatric patients.

It is well known that the efficacy of β-lactam antibiotics most strongly relates to the time during which the unbound drug concentration (*f*T) is above the pathogen MIC of the pathogen. The target pharmacokinetic/pharmacodynamics (PK/PD) index (i.e. $fT_{>MIC}$) associated with positive clinical outcomes for β-lactams in critically ill patients is a $fT_{>MIC}$ between 50% to 100% of the dosing interval.[3] Recent studies reported the PK/PD efficacy index for the β-lactamase inhibitor (BLI) tazobactam to be the percentage of time during which the unbound concentration remains above a threshold concentration ($fT{>}C_T$).[4,5] $fT{>}C_T$ targets ranged from 35 to 85% of the dosing interval, depending on the antibiotic-BLI combination and stability of the β-lactamase. Threshold concentration targets were thought to depend on β-lactamase transcription level, with upper limits of 4 mg/L used.[5,6]

Piperacillin and tazobactam are predominantly excreted in unchanged form by glomerular filtration and tubular secretion (piperacillin: 46 to 73%; tazobactam: 65 to 80%).[7] In addition, saturable renal elimination has been identified previously in adults.[8–10] To date, the pharmacokinetics of piperacillin/tazobactam have been described in (pre)term neonates and non-ICU children, but only in a small number of children admitted to the paediatric ICU (n=13

and n=12 patients), between 1 and 9 years of age.[7,11–15] Any effort to define the dose rationale in infants and young children needs to account for the effect of developmental processes, which are known to affect drug exposure and potentially treatment response.[16] Moreover, the impact of pathophysiological changes on pharmacokinetics has been widely demonstrated in critically ill adults.[17–19] The aims of this study were therefore (i) to investigate the pharmacokinetics of intravenous piperacillin and tazobactam in critically ill infants and children, and (ii) to revisit the dose rationale of the drug combination and evaluate the efficacy of current and alternative dosing regimens in this population based on PK/PD indices.

PATIENTS AND METHODS

Study design and ethics

A prospective, pharmacokinetic study was conducted at the paediatric ICU unit of the Ghent University Hospital, Ghent, Belgium between May 2012 and March 2014. Patients between 1 month and 15 years of age admitted to the paediatric ICU in whom treatment with intravenous piperacillin/tazobactam was clinically indicated, were included. Patients were excluded if they required an extracorporeal circuit or did not have, other than the drug infusion line, an arterial or intravenous access available for blood sampling. The research was conducted in accordance with the guidelines of the Declaration of Helsinki, was approved by the institutional Ethics Committee (EC/2012/172) and was registered at Clinicaltrials.gov (NCT02456974). Written informed consent was obtained from the parents or legal representatives as well as assent from patients older than 12 years. Collected demographic and clinical variables included: body weight (WT), postmenstrual age (PMA), primary reason for admission, measures of organ function and patient severity of illness as described by the PELOD (Pediatric Logistic Organ Dysfunction) Score, PRISM II (Pediatric Risk of Mortality) Score, type of catheter used for

drug administration and blood sampling, presence of mechanical ventilation, co-treatment with vasopressors and nephrotoxic medications (amikacin, ibuprofen, diclofenac, vancomycin, teicoplanin), presence of surgery, fluid resuscitation (>60 mL/kg per 24 hour), and C-Reactive Protein (CRP).[20,21]

Drug dosing and administration

Piperacillin/tazobactam (Tazocin® 2 g/250 mg and Tazocin® 4 g/500 mg, Pfizer, Belgium) was prescribed in a dose of 75 mg piperacillin per kilogram body weight (maximum 4000 mg) every 6 hours and administered intravenously over 5 to 30 minutes using a calibrated syringe driver, according to current dosing guidelines.[22] Immediately after drug administration, infusion lines were flushed with normal saline with a minimum of twice the dead space volume.

Blood sampling

Serial blood samples were obtained from 1st and/or assumed steady-state doses from an indwelling catheter other than the drug infusion line. The total number of samples collected (per individual patient) was limited by the predefined total maximum blood volume permitted for PK sampling (i.e. 2.4 mL/kg body weight).[23] A typical sampling scheme included blood sampling just before dosing (t=0), immediately after dosing and flush, between 5 and 70 min after the start of the infusion, at 3 hours after the start of the infusion and a trough sample just prior to the next dose. All samples were immediately transferred on ice to the chemistry laboratory and centrifuged (8 minutes, 1885g) after which the resulting plasma was frozen at -80°C for a maximum of 3 months before assay.

Drug and biochemical assays

Piperacillin and tazobactam total plasma concentrations were quantified simultaneously using a validated UPLC-tandem mass spectrometry method.[24] The lower limit of quantification (LLOQ) was 0.5 mg/L for both compounds and the imprecision was < 15% at all levels. For the first 29 patients, only the piperacillin compound was quantified. Plasma Cystatin C (CysC)

was measured using the N Latex cystatin C assay on the Behring Nephelometer II (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) (intra-assay coefficient of variation [CV]: 1.4%; inter-assay CV: 5.4%) and was standardized according to the ERM-DA471/IFCC reference material.[25] Creatinine was measured in serum (Scr) using the rate-blanked compensated Jaffe technique (Modular P and Cobas 6000, Roche Diagnostics GmbH, Mannheim, Germany).

Pharmacokinetic analysis

The pharmacokinetics of piperacillin/tazobactam was evaluated using non-linear mixed effects modelling. Data were analysed using the first-order conditional estimation method with the interaction option (FOCE-I), as implemented in NONMEM version 7.2 (ICON PLC; Ellicott City, Maryland). R (version 3.1.1) and PsN (version 3.5.3) were used for pre- and post-processing of the data as well as the creation of graphical and statistical summaries. One-, two-, and three-compartment disposition models with zero order input were tested to characterize the time course of plasma concentrations of both compounds independently using the ADVAN subroutines.[26] For piperacillin, first-order (FO), Michaelis-Menten (MM) and FO+MM elimination were also evaluated. A decrease in objective function value (OFV) of 3.84 points ($p<0.05$) or more was considered statistically significant assuming a χ^2 distribution for nested models. Goodness-of-fit included visual inspection of the following plots: observed versus population predicted concentrations, observed versus individual predicted concentrations, conditional weighted residuals versus time, conditional weighted residuals versus population predicted concentrations.

A log-normal distribution was assumed for the between-subject variability (BSV), whereas additive and proportional models (and a combination of both) were tested to describe residual variability in the data. Interoccasion variability (IOV) was tested on clearance and central volume of distribution of piperacillin.

Covariate model building

Continuous covariates were evaluated using a linear or exponential equation (equation 1):

$$P_i = P_{pop} \times \left(\frac{COV}{median\ (COV)}\right)^k (1)$$

In this equation P_i represents the individual parameter estimate of the ith subject, P_{pop} represents the population parameter estimate, COV is the covariate of interest and k the exponent which is fixed to 1 for a linear function and estimated for an exponential function.

Binary covariates were tested using the following equation (equation 2):

$$P_i = P_{pop} \times (1 + m_i) (2)$$

where m was estimated for one of the dichotomic covariate values (e.g. males).

Body weight was *a priori* included as a covariate using a power function with a fixed exponent of 0.75 on clearance and 1 on volume parameters. Furthermore, as children below the age of 2 years were included, a Hill function based on postmenstrual age was tested to describe maturation on clearance (equation 3):

$$F_{mat} = \frac{PMA^{HILL}}{TM_{50}{}^{HILL} + PMA^{HILL}} (3)$$

where F_{mat} represents the maturation function, PMA the postmenstrual age, Hill the Hill coefficient describing the steepness of the function, and TM_{50} the maturation half-life.[27]

The potential impact of remaining covariates was explored by visual inspection of post-hoc individual PK parameter estimates and deviations from population-predicted PK

parameters (ETAs) versus covariate plots. Only clinically relevant associations were considered: gender, serum cystatin C, PELOD score, PRISM score, admission reason and co-medication related covariates for clearance, and age, gender, PELOD score, PRISM score and admission reason for volumes of distribution.

To account for the age effect in serum cystatin C values, data from Fischbach *et al.* and Randers *et al.* were used as reference (i.e. typical value) for each age ($T_{cystatin\ C}$). [28,29] An exponential decline was found, according to following equation (equation 4):

$$T_{cystatin\ C} = 1.598 \times e^{-0.624 \times age\ (years)} \quad (4)$$

Above the age of 1.3 years, a typical constant value of 0.8 mg/L was used.

Possible influence of serum cystatin C on clearance was subsequently evaluated using measured serum cystatin C values ($M_{cystatin\ C}$) and according to following equation (equation 5):

$$\left(\frac{M_{cystatin\ C}}{T_{cystatin\ C}}\right)^{n} \quad (5)$$

Scr could not be evaluated as potential covariates on clearance, given 39% of Scr samples were below quantification limit (BQL). Selected covariates were then separately entered into the model and evaluated by use of OFV via forward inclusion ($p<0.05$) and backwards elimination methods ($p<0.001$). In addition, a clinically relevant reduction in the magnitude of BSV on the parameter of interest, acceptable precision of the model parameters, and visual inspection of the goodness-of-fit plots were used to support the additional inclusion of additional covariates into the model.

Model evaluation

Model performance, stability and robustness were evaluated using a nonparametric bootstrap analysis (n=1000 samples), a prediction-corrected visual predictive check (pcVPC) stratified for weight (n=1000 simulations), and the normalised prediction distribution error (NPDE) (n=1000 simulations).[30,31]

PTA simulation analysis

Monte Carlo simulations were performed to simulate piperacillin and tazobactam exposures for 3500 patients (**Table 1**).[22,32] The simulation dataset was created using a function described by Sumpter *et al*., in order to simulate weights based on postmenstrual age and sex, evenly distributed within the age range of our patient population (n=250 boys and 250 girls each, for the age categories 1 to 6 monts, 6 months to 1 year, 1 to 2 years, 2 to 4 years, 4 to 8 years, 8 to 12 years, 12 to 15 years).[33]

Based on these simulations, $fT_{>MIC}$ and $fT{>}C_T$ were calculated for the first 48 hours of treatment, as early and appropriate therapy is most critical.[34] The target efficacy exposure for piperacillin was defined as 60% $fT_{>MIC}$ and PTA was calculated for MICs between 1 to 64 mg/L.[16] A PTA $\geq$ 90% was defined as optimal. To evaluate proposed dosing regimens, an infection with *Pseudomonas aeruginosa* and MIC of 16 mg/L was used, according to the EUCAST breakpoint for piperacillin.[35] For tazobactam, the reference target efficacy exposure values included 40, 60 and 80% $fT{>}C_T$ and PTA was calculated for C_Ts between 0.25 and 8 mg/L. Given that tazobactam is given in a fixed combination with piperacillin (ratio 8:1), only those dosing regimens with a PTA$\geq$90% for piperacillin were appraised **(Table 1)**. Mean protein binding of piperacillin and tazobactam is 30%, and this was used to simulate unbound concentrations.[36]

RESULTS

A total of 47 patients were included; demographic, clinical and treatment characteristics are summarized in **Table 2**. Patients younger than 2 years accounted for 42.5% of the study population (n=20). Of a total of 317 piperacillin and 125 tazobactam plasma samples collected, 7 piperacillin (2%) and 4 tazobactam (3%) concentrations were excluded from pharmacokinetic analysis due to sampling errors. Median number of samples available for analysis per patient was 7 for piperacillin and 6 for tazobactam.

A two-compartment model with first-order elimination best described the data of both piperacillin and tazobactam. BSV for piperacillin and tazobactam was described using an exponential model and was identified on clearance and all volume parameters. A proportional error model was used to describe residual variability for both compounds. Neither saturable elimination nor IOV on clearance and volume of distribution was identified on piperacillin. BSV on the central volume of distribution of the piperacillin compound was estimated to be close to a value of 0 after inclusion of allometric scaling. No significant change in OFV was noted when it was fixed to 0 for subsequent model building steps. Implementation of a concomitant vancomycin treatment covariate on piperacillin clearance resulted in a drop in OFV of 18.57 points with a marginal decrease of BSV on clearance. With only six individuals receiving vancomycin, and a potential confounding by age differences between those who received vancomycin and those who did not (median age [range] 4.71 [3.08-11.92] years, versus 2.17 [0.17-15] years), this covariate was not included in the final model. In addition, the more parsimonious final model incorporating weight and PMA as described above performed reasonably well, with only slight deviations in the higher concentration range (**Figure 1A-B**). No other collected clinical variables were deemed necessary for further statistical covariate testing, based on visual inspection of the covariate plots.

The final covariate equations, population PK parameter estimates and their precision are summarized in **Table 3**. All structural model parameters were estimated with adequate

precision, which was further confirmed with the bootstrap analysis. The pcVPC plots are presented in **Figure 2**; the 5^{th}, 50^{th} and 95^{th} percentiles of the predicted concentrations closely follow the percentiles of the observed data, suggesting a good model fit in both cases. The NPDE mean and variance were not significantly different from 0 and 1, respectively ($p>0.1$) (Figure not shown).

The PTA for piperacillin by MIC after 48h of treatment for different dosing scenarios (**Table 1**) are presented in **Figure 3** (intermittent dosing) and **Figure 4** (continuous dosing regimens). With a MIC value of 16 mg/L, PTA for intermittent dosing regimens ranged from 5.9% (75 mg/kg piperacillin every 8 h, 15 min infusion) to 99% (100 mg/kg piperacillin every 4 h, 2 hour infusion). Three intermittent dosing regimens met the PTA criterion of 90% (75 mg/kg piperacillin every 4 h, infusion over 2 h; 100 mg/kg every 4 h over 1-2 h). For all continuous dosing regimens, PTA was 100% for the time after the loading dose.

PTA for tazobactam by C_T after 48h of treatment are presented in **Figure S1** (selection of intermittent dosing regimens with PTA>90% for piperacillin) and **Figure S2** (continuous dosing regimens). For a C_T below 2 mg/L, PTA was >90% for all selected intermittent dosing scenarios, regardless of the target $fT>C_T$ (12.5 mg/kg tazobactam every 4h, 1-2h infusion, 9.375 mg/kg every 4h, 2h infusion). For all continuous dosing regimens, PTA for a C_T of 4 mg/L was 100% for the time after the loading dose, regardless of the target $fT>C_T$.

DISCUSSION

This is, to our knowledge, the largest study to date in which the pharmacokinetics of piperacillin and tazobactam has been characterized in critically ill infants and children (n=47). This is also the first time that pharmacokinetic data have been collected in children between the ages of 2 months and 1 year (n=14) and 9 and 15 years (n=10).

Of note is the fact that we have characterized the effect of growth and organ maturation on the pharmacokinetics of both compounds, as demonstrated by the functions describing the clearance of both piperacillin and tazobactam. A similar model describing the effect of organ maturation was proposed by Tornoe *et al.*, who analysed pooled data from hospitalized children with a suspected or proven infection, and Rhodin *et al.*, who described the maturation on glomerular filtration rate.[37,38] The maturation half-life, which is the age associated with 50% maturation of clearance, and the age associated with full maturation in our study were 5.5 months and 4.8 years, respectively (**Table 3**). These estimates were significantly lower than previously reported by the forementioned authors, (maturation half-life: 2.2 months; full maturation around 2 years of age) and suggest that critical illness could cause a (temporary) impairment of the underlying renal maturation process.[37,38]

When comparing the maturation parameter estimates of piperacillin versus tazobactam in our population, it seems that maturation of tazobactam clearance was less affected when compared to piperacillin clearance, with a maturation half-life and age of full-maturation closer to Tornoe and Rhodin estimates.[37,38] Although more data from neonates and infants are needed to estimate maturation more accurately, these observations raise questions about the impact of fixed-dose combinations of piperacillin/tazobactam in seriously ill young children.

Since both compounds are renally cleared, one cannot exclude the role of organ function on the elimination of either compound. Hence, while the relationship between markers of renal function is plausible and expected, variations in drug clearances in this group of patients were captured primarily by body weight and the maturation function, which is in agreement with findings from previous studies in critically ill children.[14,15]

Cystatin C is a low molecular weight protein which is completely filtered through the glomeruli, rendering it a promising biomarker for measuring Glomerular Filtration Rate (GFR) in children. Recently, it was found to predict elimination of the renally cleared

amoxicillin/clavulanic acid with a similar covariate model as ours, in a comparable population PK study in critically ill children (n=50 patients).[39] One could only speculate why, in this study, we were not able to identify cystatin C as a drug clearance descriptor. Potential explanations include (i) serum cystatin C may be affected by the underlying disease (septic conditions), which may mask the effect of age on organ function (i.e., GFR), (ii) too narrow variation in cystatin levels to identify a statistically significant correlation, since no patients with renal insufficiency were included, (iii) both compounds are cleared substantially more through tubular secretion (besides glomerular filtration), when compared to amoxicillin/clavulanic acid. As mentioned previously, we were not able to evaluate serum creatinine (and estimated glomerular filtration rate based on serum creatinine) as a potential covariate due to the large portion of BQL values. In this study, the Jaffe reaction was used for creatinine bio-analysis, a method which is still very popular due to its simplicity and low cost. Due to a standardisation of creatinine measurements in 2006, analyzers automatically now correct through the use of a fixed correction factor to adjust for interfering protein content in adults. Unfortunately, due to lower total protein reference ranges, this overcorrection can potentially lead to undetectable creatinine levels in infants and children.[40] No further clinically relevant covariates on PK parameters were found.

As β-lactam antibiotics are time-dependent antibiotics with $fT_{>MIC}$ the PK/PD parameter of interest, drug clearance is the most important PK parameter related with adequate exposure. The observed population estimate for piperacillin clearance (0.25 L/h/kg) is within the observed range in 47 non-ICU children (0.20-0.35 L/h/kg) and comparable to what has been observed in 16 critically ill adults with hyperfiltration (0.25 L/h/kg).[7,41] It is noticeably higher (>20%) when compared to studies in neonates (0.08-0.14 L/h/kg), non-ICU oncology children (0.20 L/h/kg), healthy adults (0.14-0.16 L/h/kg), and a cohort of 12 critically ill children (0.20 L/h/kg), but substantially lower (>20%) than observed in another cohort of 13 critically ill

children (0.30 L/h/kg).[10,11,13-15,42] The observed tazobactam clearance (0.13 L/h/kg) is lower to what has previously been observed in children of the same age.[7,15] Despite the limitations for a direct comparison of the results, disease-driven changes in drug disposition can have major impact on drug clearance. In several subpopulations of critically ill adults, augmented renal clearance (ARC) of antibiotics leading to subtherapeutic concentrations has been extensively described.[43] Despite increasing appreciation of this phenomenon, scarce data are available in children receiving β-lactam antibiotics.[14,40,44]

In our study population clearance values higher than expected were observed in some patients with observed individual piperacillin clearances up to 0.35 L/h/kg. We hypothesize that such an apparent variation in clearance results from an increase in renal blood flow, leading to hyperfiltration in those patients with sepsis. The hypothesis of ARC was also supported by the fact that a large proportion of measured renal biomarkers was undetectable (Scr) or low (CysC) compared to age-corrected reference values.[45] A plausible explanation, besides the analytical challenges for creatinine described above, could be a faster renal clearance of these endogenous compounds. Moreover, trough concentrations from maintenance doses remained very low in most patients. This phenomenon suggests that no accumulation occurs during steady-state conditions, probably due to the enhanced renal capacity. Although our study was not powered for the evaluation of efficacy, we speculate that children admitted to the ICU with lower disease severity and organ failure scores are most at risk for ARC and subsequent subtherapeutic antibiotic concentrations, as previously observed in adults.[41] Notably, children admitted to a general paediatric ward, may also experience ARC since high piperacillin clearances (upper range of 0.35 L/h/kg) have also been reported in non-ICU children with suspected or proven infection.[7] Further investigation is needed to identify patient risk factors for developing hyperfiltration in children.

Regarding the observed population estimate of volume of distribution for piperacillin (0.25 L/kg), our observation is within the observed range in non-ICU children (0.24-0.33 L/kg). It is noticeably higher (>20%) when compared to healthy adults (0.14-0.18 L/kg) but substantially lower than reported in (pre-)term neonates (0.37-0.42 L/kg), non-ICU oncology children (0.41 L/kg, two other studies in critically ill children (0.43-0.55 L/kg) and critically ill adults (0.35 L/kg).[7,11-15,41] The observed volume of distribution of tazobactam (0.24 L/kg) is lower to what has previously been observed in children of the same age (0.30-0.39 L/kg).[7,15] Also here, it is unclear whether these differences in volume of distribution are due to differences in body composition of the study population (e.g. larger total and extracellular body water content in neonates compared to infants and children), differences in disease severity (e.g. vascular leakage), and/or different sampling and PK parameter estimation methods.

Treating infections in the seriously ill child without evidence-based dosing recommendations remains a huge challenge and may lead to an increased morbidity and mortality.[46] Our analysis challenges currently used dosing regimens (75-100 mg/kg piperacillin every 6 to 8 hours, given as a short infusion), as they only yield a PTA between 5.9 to 34% for piperacillin, thereby potentially leading to subtherapeutic treatment (**Figure 3**).[14] These findings of underdosing are consistent with previously reported exposure data in critically ill children of the same age.[14,15]

For the treatment of Pseudomonas infections, no clear-cut $fT>C_T$ target values are available for tazobactam, in combination with piperacillin. Therefore, we performed a PTA analysis appraising different targets (20-60-80% $fT>C_T$) (**Figure S1, S2**). The choice was based on the only properly designed *in vitro* study in which the pharmacodynamics of tazobactam was characterised in combination with piperacillin.[5] Further studies are required to confirm the appropriate target. Our analysis should be interpreted with caution, but it does provide insight into how differences in exposure may affect antimicrobial response.

More frequent dosing, prolonged infusions and continuous infusions have been proposed as dose optimization strategies for β-lactam antibiotic treatment.[47] However, it should be noted that, we have specifically chosen not to select higher amounts per dose for intermittent dosing regimens (max. 100/12.5 mg per kg piperacillin/tazobactam) than currently recommended. This was done to mitigate potential safety risks related to higher peak concentrations, thereby avoiding the potential for saturation of the elimination processes which determine the clearance of piperacillin. This 'same amount per dose' approach should also prevent a higher degree of reduced tazobactam clearance, as it is known that both piperacillin and tazobactam interact by a competitive inhibition at the level of the tubular anion transporter system.[48] Regarding the safety of continuous infusions, Delvallée *et al.* reported the use of a 400 mg/kg/day infusion on a paediatric haematology unit without any observed adverse events.[44]

Our simulations showed that, four hourly dosing regimens (given as a prolonged infusion), and all continuous dosing regimens met the PTA criterion for piperacillin (**Figure 3,4**). Despite the higher PTA with these prolonged and continuous infusions, we acknowledge that these dosing regimens may have important implications on drug administration practices, as intravascular access is frequently limited and drug incompatibilities with piperacillin/tazobactam often occur.[47,49] Therefore, a rational choice in dosing regimen is advised, depending on the individual patient characteristics, site of infection and target MIC. In our opinion, prolonged and continuous infusions seem a preferable option whenever possible, especially when antibiotic therapy is started empirically or when higher $fT_{>MIC}$ targets are needed (e.g. neutropenic children).

This research has some notable limitations. First, the studied population included a heterogeneous group of children with regard to possible differences in (suspected) infecting organism and tissue involvement/penetration. Second, total drug plasma concentrations were

mathematically corrected for protein binding instead of free drug concentration measurement in plasma, or drug measurement at the site of infection. However, this simplification was previously found to be acceptable for β-lactam antibiotics with low protein binding like piperacillin and tazobactam.[50] Third, MIC values were not prospectively determined in order to be able to calculate individual target drug concentrations in culture-proven infections. Instead, a worst-case scenario using the clinical breakpoints for *P. aeruginosa* was chosen as reference to explore dosing regimens by $fT>C_T$. This approach is suitable for β-lactam antibiotics and tazobactam, which are known to have a wide therapeutic index. Consequently, there should be limited concern about potentially supra-therapeutic dosing. Moreover, from our simulation studies, we concluded that there is no risk for accumulation of piperacillin and tazobactam, when using any of the alternative dosing scenarios (**Table 2**). Fourth, notwithstanding that a substantial number of younger patients were recruited, more extensive PK data from neonates and infants are needed to estimate maturation parameters more precisely on both clearances and refine dosing regimens in these age categories.

In conclusion, our study shows that current dosing recommendations for piperacillin and tazobactam can result in subtherapeutic treatment in critically ill children, thereby risking treatment failure. We proposed alternative, model-based dosing regimens that increase the PTA from 5.9 to 100 % for *P. aeruginosa* infections with a MIC of 16. A prospective, randomized controlled trial evaluating efficacy and safety for the proposed optimized dosing strategies may be required to further substantiate these results.

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Transparency declarations

None to declare.

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Table 1. Simulated dosing scenarios

Intermittent dosing regimen[a]	**Infusion duration**
75 mg/kg every 4 hours	0.25, 0.5, 1, 2 hour(s)
75 mg/kg every 6 hours	0.25, 0.5, 1, 2 hour(s)
75 mg/kg every 8 hours	0.25, 0.5, 1, 2 hour(s)
100 mg/kg every 4 hours	0.25, 0.5, 1, 2 hour(s)
100 mg/kg every 6 hours	0.25, 0.5, 1, 2 hour(s)
100 mg/kg every 8 hours	0.25, 0.5, 1, 2 hour(s)
Continuous infusion dosing regimen[a]	
LD of 75 mg/kg over 1 hour, followed by CI 300 mg/kg over 24 hours	
LD of 75 mg/kg over 1 hour, followed by CI 350 mg/kg over 24 hours	
LD of 75 mg/kg over 1 hour, followed by CI 400 mg/kg over 24 hours	

[a]based on piperacillin component and a fixed ratio of piperacillin:tazobactam of 8:1

Abbreviations: LD: loading dose; CI: continuous infusion

Table 2. Demographic and clinical characteristics of the study population

Variable[a]	**Median (range)**
Gender	
Male	21 (44.7%)
female	26 (55.3%)
Age (years)	2.83 (0.17-15)
Weight (kg)	14 (3.40-45)
PRISM II score	8 (0-40)
Primary reason for ICU admission	
respiratory	11 (23.4)
gastro-intestinal	10 (21.3)
neurologic	7 (14.9)
postoperative	7 (14.9)
cardiovascular	7 (14.9)
burn	2 (4.3)
oncology	1 (2)
other	2 (4.3)
Mechanical ventilation[c]	25 (53.2)
Vasopressor treatment[c]	15 (31.9)
PELOD score[d]	1 (0-32)
Serum Creatinine (mg/dL)[d,e]	0.21(<0.17-0.55)
Plasma Cystatin C[d,e] (mg/L)	0.66 (0.38-1.13)
Serum CRP[f] (mg/L)	7.8 (0.1-147)

[a]Abbreviations: PRISM, Pediatric Risk of Mortality; PELOD, Pediatric Logistic Organ Dysfunction; CRP, C-Reactive Protein

[c]during ICU stay; [d]at day(s) of sampling; [e] below quantification limit in 14 patients; [f]based on values from 44 patients.

Table 3. Population Pharmacokinetic Estimates of Piperacillin/tazobactam

	Piperacillin					**Tazobactam**				
	Estimate	**RSE (%)**	**Bootstrap estimates (n=1000)[a]**			**Estimate**	**RSE (%)**	**Bootstrap estimates (n=1000)[a]**		
			Median	*Percentile 2.5%*	*97.5%*			*Median*	*Percentile 2.5%*	*97.5%*
Structural model parameters										
$CL_i = CL_{pop} \times \left(\frac{WT}{14}\right)^{0.75} \times \left(PMA^{HILL}/TM_{50}{}^{HILL} + PMA^{HILL}\right)$										
CL(L/h)	4.00 (0.25)[b]	8	4.04	3.50	5.50	3.01 (0.13)[b]	5	3.01	2.72	3.33
TM_{50} (weeks)	61.2	15	62.5	46.2	126	41.2	11	41.7	33.6	51.31
Hill coefficient	1.62	27	1.60	0.74	2.84	2.96	31	3.10	1.41	14.3
$Q_i = Q_{pop} \times \left(\frac{WT}{14}\right)^{0.75}$										
Q (L/h)	2.72 (0.19)[b]	14	2.68	2.06	3.78	2.11 (0.15)[b]	28	2.18	1.34	6.64
$V_i = V_{pop} \times \left(\frac{WT}{14}\right)^{1}$										
V1 (L)	1.80 (0.13)[b]	5	1.80	1.63	1.99	1.86 (0.13)[b]	12	1.82	1.19	2.15
V2 (L)	1.59 (0.11)[b]	9	1.58	1.35	1.92	1.58 (0.11)[b]	16	1.59	1.19	2.51
Between-subject variability										
BSV CL (% CV)	26.7	25	25.5	18.5	31.3	14.5	29	11.7	3.92	19.8

BSV V_1 (% CV)	0[d]	-	-	-	-	41.1	14	41.0	21.4	57.6
BSV Q (% CV)	0[d]	-	-	-	-	0[d]	-	-	-	-
BSV V_2 (% CV)	22.6	72	22.9	8.42	37.8	27	21	26.1	12.9	36.5
Residual variability										
Proportional (% CV)	31.0	14	30.5	26.5	34.6	30.5	20	30.2	24.0	36.6
Additive (mg/L)	0.0001[c]	-	-	-	-	0.0001[c]	-	-	-	-

[a]non-parametric bootstrap: 969 runs mimization successful for piperacillin; 850 runs minimization succesful for tazobactam;[b]parameters per kg body weight; [c]fixed value

Abbreviations: CL_i, individual clearance; CL_{pop}, population clearance; WT_{med}, median weight; PMA, postmenstrual age; TM_{50}, maturation half-life; Hill, Hill coefficient; Q, intercompartmental clearance; BSV, between-subject variability; RSE, relative standard error

Figure 1A. Goodness-of-fit diagnostic plots for piperacillin: observations versus population predictions and individual predictions and conditional weighted residuals (CWRES) versus time after dose and population predictions.

Figure 1B. Goodness-of-fit diagnostic plots for tazobactam: observations versus population predictions and individual predictions and conditional weighted residuals (CWRES) versus time after dose and population predictions.

Figure 2. Prediction-corrected visual predictive check (n= 1000 simulations) for piperacillin (left panel) and tazobactam (right panel): grey shaded areas are 95% confidence intervals of simulated 5th, 50th and 95th percentiles, lines are 5th, 50th and 95th percentiles of raw data.

Figure 3. PTA for piperacillin (n=3500 patients) according to following intermittent dosing regimens : (A) 75 mg/kg every 4, 6, 8 hours or 100 mg/kg every 4, 6, 8 hours over 0.25 hours, (B) 75 mg/kg or 100 mg/kg every 4, 6, 8 hours over 0.5 hour, (C) 75 mg/kg or 100 mg/kg every 4, 6, 8 hours over 1 hour, (D) 75 mg/kg or 100 mg/kg every 4, 6, 8 hours over 2 hours. Piperacillin target was defined as 50% of time above a MIC of 16 mg/L. The solid horizontal line represents 90%.

Figure 4. PTA for piperacillin (n=3500 patients) according to following continuous dosing regimens : loading dose of 75 mg/kg over 1h, followed by (i) a continuous infusion (CI) of 300 mg/kg/24h, (ii) CI of 350 mg/kg/24h, (iii) CI of 400 mg/kg/24h. Piperacillin target was defined as 50% of time above a MIC of 16 mg/L. The solid horizontal line represents 90%.